

EXHIBIT M

ATTACHMENT D

United States Patent [19]

Gallagher, Jr.

[11] 4,452,808

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[54] 4-AMINOALKYL-2(3H)-INDOLONES

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[52] U.S. Cl. 424/274; 548/486

[58] Field of Search 548/486; 424/274

[36] References Cited

U.S. PATENT DOCUMENTS

3,373,310 3/1971 Van Dyke 548/486
4,317,944 2/1982 Huffman et al.

FOREIGN PATENT DOCUMENTS

895875 3/1972 Canada 548/486

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[57] ABSTRACT

A series of new chemical compounds which are 4-aminoalkyl-2(3H)-indolones has been demonstrated to be D₂-agonists useful for treating hypertension. A representative compound of the series is 4-di-n-propylaminoethyl-2(3H)-indolone.

12 Claims, No Drawings

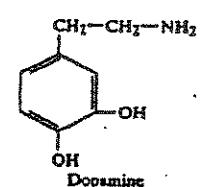
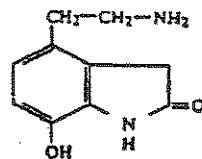
4-AMINOALKYL-2(3H)-INDOLONES

This invention relates to certain novel 4-aminoalkyl-2(3H)-indolones as well as to anti-hypertensive compositions and methods which use them.

BACKGROUND OF THE INVENTION

4-Aminosalkyl-7-hydroxy-2(3H)-indolones are described in U.S. Pat. No. 4,314,944 to have a beneficial effect on abnormal conditions of the cardiovascular system. More specifically, such compounds are said to have a vasodilatation effect on the kidney which is similar to that of dopamine, thereby inducing anti-hypertensive activity due to a dopaminergic mechanism.

The basic structure of the prior art compounds is similar to that of the well known cardiovascular agent they mimic, dopamine:

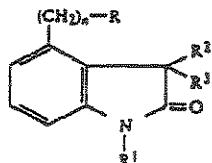


One skilled in the structure function art will appreciate that the 7-hydroxy group of the compounds of the prior art is necessary for them to resemble the structure of dopamine. Without this key group, the resulting compounds would not be expected to have cardiovascular activity.

DESCRIPTION OF THE INVENTION

The indolone compounds of this invention have beneficial cardiovascular activity despite the lack of the supposedly essential 7-hydroxy group. In addition to not having a catechol or catechol-mimicking structure, these indolones may not be subject to tachyphylaxis and are better absorbed orally when compared with the prior art compounds based on preliminary pharmacological tests with the preferred species of this invention.

The compounds are illustrated by the following structural formula:



in which:

R is amino, lower alkylamino, di-lower alkylamino, allylamino, diallylamino, N-lower alkyl-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphen-

thylamino, 4-hydroxyphenethylamino or di-(4-hydroxyphenethylamino);

R¹, R² or R³ are, each, hydrogen or lower alkyl; and n is 1-3.

A subgeneric group of this invention comprises the compounds of formula I in which:

R is amino, di-n-propylamino, n-propyl-n-butylamino or 4-hydroxyphenethylamino;

R¹, R² or R³ are hydrogen; and

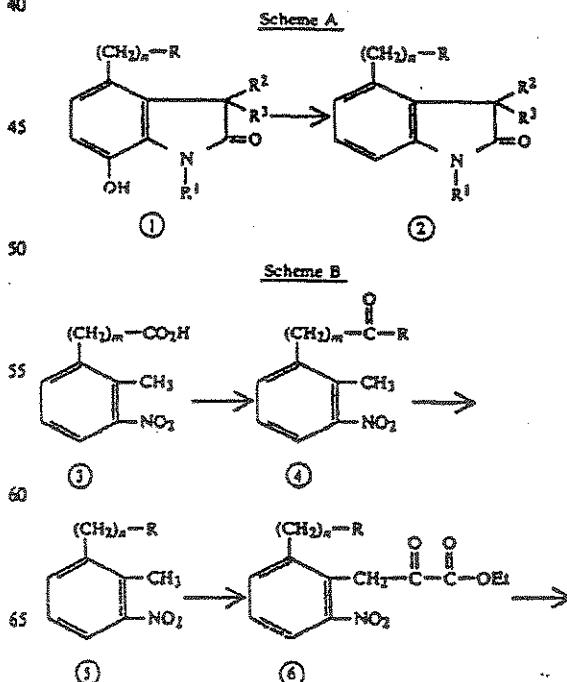
(CH₂)_n is ethylene (-CH₂-CH₂-).

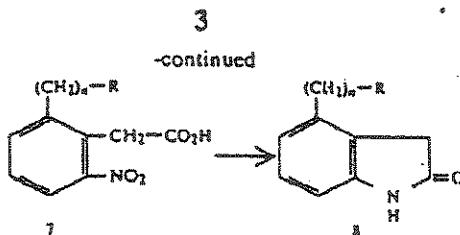
A preferred species of this invention is 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or one of its pharmaceutically acceptable, acid addition salts.

The term "lower alkyl" used herein and in the claims is meant, for convenience, to include branched and straight chain groups of from 1-6 carbons, preferably n-propyl, for each alkyl in R and from 1-4 carbons, preferably methyl, for each of R¹, R² and R³. R¹, R² and R³ are preferably, for ease of preparation, all the same.

The pharmaceutically acceptable acid addition salts having the utility of the free bases of formula I are part of this invention. These are prepared by methods well known to the art and are formed with both inorganic or organic acids, for example: maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethyleneasicylic, methanesulfonic, ethane disulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfonic, phosphoric and nitric acids. The hydrohalic and, especially, methane sulfonic acid salts are conveniently used.

The compounds of this invention are prepared by the following reaction sequences:





In the reaction sequences of Schemes A and B above, n , R , R^1 , R^2 and R^3 are as described for formula I; m is $n-1$. In some cases, such as where R is a primary or secondary amino, a protective group may be present, as described in more detail below.

In addition to the reaction sequences noted above, the compounds of this invention are prepared by the reactions which are described in U.S. Pat. No. 4,314,944, using, of course, known deshydroxy or desmethoxy starting materials. In preparing the present 7-unsubstituted indolones by this route, the ring closure to form the isatin ring at column 2 of that patent can proceed to give two isomeric products which must then be separated to yield the indolones of this invention.

In Scheme A, the corresponding 7-hydroxy indolone starting material (1) is de-hydroxylated by reacting it with at least a stoichiometric quantity of a reactive 5-halo-1-phenyl-1H-tetrazole in the presence of an acid binding agent, such as an alkali metal carbonate, in a suitable inert solvent, such as aqueous acetone, dimethylformamide or dimethylacetamide. The reaction is carried out at room temperature until substantially complete. From one to two days may be used. If desired, the reaction may be carried out in shorter time by operating at a higher temperature, for example, up to 75°.

The resulting new intermediate, a 4-(aminoalkyl)-7-(1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone, is subjected to hydrogenation to split the tetrazole-oxyindolone link. Conveniently, catalytic hydrogenation, for example using a noble metal catalyst at moderate pressures of hydrogen and some heat, such as palladium-on-charcoal at 50° for 20 hours under 55 p.s.i. is used.

When R is a reactive amino, the starting material (1) is used in the form of an acid addition salt or an otherwise amino protected derivative. If a hydrogenation labile protective group is present on compound 1, it is also split during the reduction.

The reactions of Sequence B involve the insertion of the aminoalkyl side chain into the phenyl ring (1-7) followed by ring closure of the *o*-carboxymethyl-*m*-nitro intermediate (7). The ring closure is carried out by reduction of the intermediate, for example, using catalytic hydrogenation over a noble metal, preferably palladium, catalyst in a suitable solvent, for example, a lower alcohol, dilute hydrochloric acid or glacial acetic acid, at moderate pressures of hydrogen and at a temperature chosen from the range of room temperature to 60°. The reaction proceeds quickly to completion. The nitro group of compound 7 is reduced first, followed by ring closure.

As noted above, this reaction sequence is adaptable to prepare the compounds having a reactive aminoalkyl side chain by protecting an amine or another reactive group with a standard protecting means such as forming a maleimide, tert. boc or phthalimide derivative, which is removed, by standard reactions, after ring closure. The phthalimido protective group, for example, is split using reaction with hydrazine hydrate. A benzyloxy is

split by using catalytic hydrogenation; a tert.-sec. using
mild acid.

The alkylated products of this invention are, alternatively, or, in certain instances, preferentially prepared by alkylation of the parent amino compounds of formula I in which R is amino or a secondary amino. For example, the N-alkylated products, formula I when R is a secondary or tertiary amino, are conveniently prepared by reductive alkylation using, for example, the aldehyde in one or two molar equivalent quantities under reduction conditions, such as under catalytic hydrogenation conditions over a palladium or platinum catalyst or such as using formaldehyde-formic acid when R is dimethylamino.

15 N-Alkylation, such as using an allyl or benzyl halide in the presence of an acid binding agent, can be used under standard mild conditions. Protecting the amide hydrogen in the ring is also used during alkylation if necessary as known to the art. Alkyl substituents at the 20 1 or 3-positions of the indolone ring are introduced by forming the lithio derivatives at the ring position, such as using butyl lithium, followed by reaction with a lower alkyl halide, especially an alkyl iodide. This process is similar to that reported by A. S. Kende et al.,
 25 *Syn. Commun.*, 12, 1 (1982).

The compounds of this invention have utility, as specific dopamine agonists, in the treatment of disorders of the cardiovascular system, especially to treat hypertension, to treat angina pectoris, to treat the symptoms of congestive heart failure or to improve kidney function.

More specifically, the compounds of this invention, especially 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride, have proved to be selective peripheral D₂-agonists. For a discussion of various agonist/antagonist activities in the dopaminergic system, one should refer to J. M. Rooyen, et al., *S. Afr. Med. J.* 59 329 (1981), or I. Caverio et al., *Life Sciences*, 31 939, 1059 (1982). Otherwise speaking, the main focus of action is at the presynaptic α -dopaminergic receptors which may also be called "D₂-receptors." Activation of the D₂-receptors on the sympathetic nerve terminals inhibits the release of noradrenaline, thereby, promoting vasodilation, among other beneficial cardiovascular actions.

45 In the perfused rabbit ear artery test [J. P. Hieble et al., Arch. Pharmacol., 309 217 (1979)], 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride had an EC₅₀ of 72 nM. It was active *in vivo* in the dog in both the cardioaccelerator nerve and perfused hind limb preparations and did not cause tachyphylaxis in the latter preparation as did its 7-hydroxy congener of the prior art. Intravenous infusion of this species of this invention in the DOCA-salt hypertensive and spontaneously hypertensive rats reduced blood pressure and heart rate. A similar but weaker effect on blood pressure and heart rate was observed with the lead compound in the renal hypertensive rat and in the normotensive rat tests. In conscious DOCA salt hypertensive rats, oral doses of 10 mg/kg of the di-n-propylaminoethyl compound demonstrated an anti-hypertensive effect. This species seems more readily absorbed from the gastrointestinal tract than is its 7-hydroxy congener.

The pharmaceutical compositions of this invention which have pharmacodynamic activity within the cardiovascular system, for example renal vasodilatation, correcting hemodynamic imbalance, anti-anginal activity, hypotensive activity and bradycardia, are prepared in conventional dosage unit forms by incorporating

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compound of formula 1, or a pharmaceutically acceptable acid addition salt thereof, into a nontoxic pharmaceutical carrier according to accepted pharmacy procedures in a nontoxic quantity sufficient to produce the desired pharmacodynamic activity in a subject, animal or human. Preferably, the compositions will contain the active ingredient in an active but nontoxic quantity selected from the range of about 50 mg to about 500 mg, preferably about 75-250 mg, of active ingredient, as the base, per dosage unit. This quantity depends on the relative potency of the base compound compared with that of the prototypal species, 4-(2-di-n-propylaminoethyl)-2(3H)-indolone, as well as on the specific biological activity desired, the route of administration, that is, whether oral or parenteral, and the condition and size of the patient.

The pharmaceutical carrier employed for the dosage units is, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate or stearic acid. Exemplary of liquid carriers are isotonic saline for parenteral use or syrup, peanut oil, olive oil or water for soft gelatin capsules. Similarly, the carrier or diluent may include any time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or admixed with a wax. Such sustained release products as well as prodrug derivatives which may be gradually metabolized to the active parent can be employed to prolong the unique biological activity of the compounds of this invention or to attack receptors at a specific location.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier for oral or rectal administration is used, the mixed preparation can be tableted, placed in a hard gelatin capsule in powder or sustained release pellet form, in a suppository or in the form of a troche or lozenge. The amount of solid carrier will vary widely but, preferably, will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampul or an aqueous or nonaqueous liquid suspension for oral administration.

The method of this invention for producing D₂-agonist activity manifests itself by inducing renal vasodilation, anti-anginal, anti-hypertensive and bradycardic activity. It comprises administering orally, rectally or parenterally to a subject in need of such activity a compound of formula 1 or a pharmaceutically acceptable acid addition salt thereof, usually combined with a pharmaceutical carrier, in a nontoxic amount sufficient to produce said activity. The route of administration may be any route which effectively transports the active compound to the cardiovascular system receptors which are to be selectively stimulated. Such routes include oral, rectal or parenteral administration, the oral route being preferred. The parenteral administration may be subcutaneous or, preferably, intravenous for critical use.

Advantageously, doses selected from the dosage unit ranges given above will be administered several times, such as from one to five times, a day. The daily dosage regimen is selected from the range of about 50 mg to about 1.0 g, preferably 200-750 mg for oral administration and 50-500 mg for parenteral administration. When the method described above is carried out, D₂-agonist activity is produced.

For an average size human using 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride as an

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active ingredient, a typical dose to show anti-hypertensive activity would be selected from the range of from about 100-250 mg of base equivalent for each dosage unit which is adapted for oral administration and which is administered orally from 1-4 times daily.

The following examples are designed solely to illustrate the preparation and use of the compounds of this invention. The temperatures are Centigrade. Other variations of these examples will be obvious to those skilled in the art.

EXAMPLE 1

A mixture of 3.44 g (9.63 mmoles) of 4-(2-di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944), 22 cc of dimethylformamide, 1.79 g (9.91 mmoles) of 5-chloro-1-phenyl-1H-tetrazole, 220 cc of acetone, 10 cc of water and 2.90 g (21 mmoles) of anhydrous potassium carbonate was refluxed for about 3 hours at which time thin layer chromatographic analysis (silica gel GF, 75-23-2 ethyl acetate-methanol-conc. ammonium hydroxide) indicated that the reaction was complete.

After cooling the reaction mixture in an ice-bath, the inorganic salts were removed by filtration and washed with acetone. The combined filtrates were concentrated in vacuo. The residual syrup was diluted with saturated brine and extracted with three portions of diethyl ether. The gathered extracts were dried over anhydrous magnesium sulfate, clarified with charcoal and treated with ethereal hydrogen chloride until precipitation was complete. The solid was slurried in diethyl ether and decanted several times, filtered and air-dried to give 3.8 g (86%) of tan 4-(2-di-n-propylaminoethyl)-7-(1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone hydrochloride. Recrystallization from 200 cc of hot acetonitrile gave 2.6 g (59%) of microcrystalline product, m.p. 245°-6°. Evaporation of the mother liquor and recrystallization of the residue from 25 cc of hot acetonitrile gave an additional 400 mg of product, m.p. 244°-5°.

A mixture of 2.64 g (5.78 mmoles) of the phenyl tetrazole ether, 200 cc of glacial acetic acid and 1.49 g of 10% palladium-on-carbon was hydrogenated in a Parr apparatus at 50 p.s.i. for 20 hours at 50°. The warm reaction mixture was filtered through glass fiber filter-paper and the catalyst washed thoroughly with hot glacial acetic acid. The filtrate was concentrated in vacuo, the pale yellow waxy residue distributed in water and ethyl acetate. After acidification of the aqueous phase with 3N hydrochloric acid, the organic phase was separated and extracted once with 1N hydrochloric acid. The combined aqueous phases were adjusted to pH 8.5 with aqueous 10% sodium hydroxide and extracted with a mixture of ethyl acetate and diethyl ether. The combined organic extract was back-washed once with saturated brine, dried over anhydrous magnesium sulfate, clarified with charcoal, treated with ethereal hydrogen chloride and evaporated to dryness in vacuo to give 1.64 g (96%) of pale yellow crystalline solid; 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride. Recrystallization from 260 cc of hot acetonitrile which was concentrated to about 50 cc gave 1.26 g (74%) of pale yellow microcrystalline powder, m.p. 240°-242°.

The hydrochloride salt (500 mg) is shaken in the presence of ether/5% sodium carbonate solution. The ether layer is separated, dried and evaporated to give the free base which is used to prepare other salt forms such as the methanesulfonate, ethanesulfonate, sulfate

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or sulfamate by reacting aliquots of the base in ether with an excess of each acid.

EXAMPLE 2

A mixture of 22.0 g (0.105 mole) of 2-methyl-3-nitrophenylacetic acid (V. Askam et al., J. Chem. Soc. (C) 1969 1935) and 25 cc of thionyl chloride was slowly heated to 75° and the copious evolution of gasses allowed to moderate. The temperature was raised and the solution was refluxed for 1 hour. The reaction was 10 concentrated in vacuo. The residual straw-colored syrup was chased several times with dry toluene, diluted with 100 cc of dry toluene and added to a cool (10°) mixture of 13 g of sodium carbonate in 150 cc of water and 150 cc of toluene containing 14.5 cc (10.6 g, 0.12 mole) of di-n-propylamine with very slow stirring. After 30 minutes, the ice-bath was removed. Stirring was continued for one hour. An additional 0.5 g of solid sodium carbonate was added to the reaction. After 15 minutes, the organic phase was separated, washed with 5% aqueous sodium carbonate followed by 2N hydrochloric acid and, finally water. The organic solution was dried over magnesium sulfate, concentrated in vacuo and pumped free of solvent to give 29.5 g of 2-methyl-3-nitrophenyl-N,N-di-n-propyl acetamide as a 25 straw-colored syrup.

The total syrup (105 mmoles) was taken up in 250 cc of anhydrous tetrahydrofuran and treated with 160 cc of 1.0 M borane in tetrahydrofuran at room temperature for 1 hour. The reaction was refluxed for 2 hours, then cooled. Excess reagent was destroyed by the cautious addition of dry methanol. This solution was concentrated in vacuo. The residual syrup was treated with 40 cc of 6N hydrochloric acid for 1 hour on the steam-bath, cooled, basified with 40% sodium hydroxide and extracted with 3 portions of ether. The combined organic phase was washed once with brine, concentrated in vacuo and distilled in a Kugelrohr apparatus at 115°-118°/0.1 mm Hg to give 21.6 g of a mobile yellow oil; 2-methyl-3-nitrophenylethyl-N,N-di-n-propyl amine.

To a solution of 2.38 g (0.103 gram atoms) of sodium metal in 52 cc of absolute ethanol at room temperature was added 18.53 g (0.07 mole) of the nitro compound in one portion, with stirring, followed by 15.42 g (0.103 mole) of diethyl oxalate. The reaction was refluxed under nitrogen for about 20 minutes, cooled, quenched on 700 cc of ice-water and acidified with 3N hydrochloric acid. This aqueous solution was washed with a small volume of ether, basified to pH 8.5 with solid sodium carbonate and extracted with 3 portions of ether. The combined ether extract was washed with saturated brine, dried over anhydrous magnesium sulfate, clarified with charcoal and concentrated in vacuo. The residue was triturated with cold petroleum ether, filtered and air-dried to give 6.0 g of ethyl 6-(2-di-n-propylaminoethyl)-2-nitrophenylpyruvate as a yellow powder. The triturate was concentrated in vacuo and distilled to give 7.3 g of recovered starting material which was recycled. In the same manner, a total of 60 three recycles provided 11.0 g of ethyl 6-(2-di-n-propylaminoethyl)-2-nitrophenylpyruvate.

A cold (10°) solution of 10.24 g (28.1 mmoles) of the pyruvate in 196 cc of 2% sodium hydroxide was treated with 5.0 cc of 30% hydrogen peroxide dropwise over 65 several minutes. The cooling bath was removed and stirring was continued for 1.5 hours during which time the reaction became much lighter in color. A small

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amount of insoluble material was removed by filtration. The pH was adjusted to 1.5 by the cautious addition (foaming) of about 12 cc of conc. hydrochloric acid. This solution was concentrated in vacuo at 45°, reconstituted with water and evaporated twice more. The residue was slurried in a minimum volume of dilute hydrochloric acid, filtered and air-dried to give 6.40 g of 2-nitro-6-(2-di-n-propylaminoethyl)-phenyl acetic acid hydrochloride as a white powder.

A mixture of 5.83 g (16.9 mmoles) of 2-nitro-6-(2-di-n-propylaminoethyl)-phenyl acetic acid hydrochloride and 0.6 g of 5% palladium-on-carbon in 250 cc of ethanol was hydrogenated at 50 p.s.i. over 5.5 hours. The catalyst was filtered, washed with ethanol, and the filtrate evaporated to dryness in vacuo. The white residue was crystallized from 550 cc of hot acetonitrile to give 3.89 g of 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride, mp 240°-2°.

Anal. Calcd. for $C_{16}H_{24}N_2O \text{ HCl}$: C, 64.74, H, 8.49; N, 9.44. Found: C, 64.82; H, 8.26; N, 9.28.

EXAMPLE 3

A mixture of 2.73 g (10.0 mmoles) of 4-(2-aminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944), 200 cc of dimethylformamide, 1.86 g (10.3 mmoles) of 5-chloro-1-phenyl-1H-tetrazole, 10 cc of water and 2.9 g (21 mmoles) of anhydrous potassium carbonate is stirred at room temperature for 2 days or until thin layer analysis indicates that no starting material remains. The reaction is filtered and the filtrate is acidified with dil. hydrochloric acid, concentrated in vacuo and the residue triturated with abs. ethanol. The triturate is clarified with charcoal and evaporated to dryness in vacuo. The hydrochloride salt of 4-(2-aminoethyl)-7-(1-phenyl-1H-tetrazol-5-yl)-2(3H)-indolone is hydrogenated directly in 200 cc of glacial acetic acid using 50% by substrate weight of 10% palladium-on-carbon at 50 p.s.i. for 20 hours at 50°. The warm reaction mixture is filtered. The catalyst is washed thoroughly with hot acetic acid. After the filtrate is concentrated in vacuo, the residue is stripped several times from dilute hydrochloric acid and crystallized from ethanol to give 4-(2-aminoethyl)-2(3H)-indolone hydrochloride.

EXAMPLE 4

A mixture of 0.5 g of 4-(2-aminoethyl)-2(3H)-indolone hydrochloride, prepared as in Example 3, 2.2 g of isobutyraldehyde, 0.3 g of 5% palladium-on-charcoal and 75 ml of glacial acetic acid is hydrogenated at 55 p.s.i. of hydrogen for 5 hours. The catalyst is separated by filtration and washed with acetic acid. The combined-mother liquor-washings is evaporated in vacuo to give a residue which is taken up in cold methanol and treated with methanolic hydrogen bromide to give, upon concentration and cooling; 4-(2-di-isobutylaminoethyl)-2(3H)-indolone hydrobromide.

EXAMPLE 5

A mixture of 0.9 g of 4-(2-aminoethyl)-2(3H)-indolone, 0.23 g of 4-benzoyloxyphenylacetaldehyde, 0.25 g of 10% palladium-on-charcoal and 100 ml of ethanol is hydrogenated at 50 p.s.i. at 50° until the uptake of hydrogen is complete. After filtration, the mother liquors are evaporated to give 4-[2(4-hydroxyphenethylamino)-ethyl]-2(3H)-indolone as the residue. This base in alcohol is treated with an excess of methylsulfonic acid to give the methylsulfonate salt.

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Repeating this reaction with 4-n-propylaminoethyl-7-hydroxy-2(3H)-indolone and butyraldehyde gives 4-n-butyl-n-propylamino-ethyl-7-hydroxy-2(3H)-indolone hydrochloride.

EXAMPLE 6

Substituting 2.2 g of 4-(3-dimethylaminopropyl)-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944) for 4-(2-di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide in Example 1 gives 4-(3-dimethylaminopropyl)-7-(1-phenyl-1H-tetrazol-5-yl oxy)-2(3H)-indolone hydrochloride and, then, 4-(3-dimethylaminopropyl)-2(3H)-indolone base as well as the ethanesulfonate salt as described above.

Substituting 4-n-propylaminoethyl-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944) gives 4-n-propylaminoethyl-2(3H)-indolone hydrochloride.

Substituting 4-dimethylaminopropyl-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944) gives 4-dimethylaminopropyl-2(3H)-indolone hydrochloride.

EXAMPLE 7

4-Aminoethyl-2(3H)-indolone (10 g) is reacted with two mole equivalents of allyl bromide and 4 equivalents of triethylamine in acetonitrile with mild heat for several hours. The reaction mixture is evaporated. The residue is suspended in water. The mixture is extracted with ethyl acetate. The extracts are washed, dried and evaporated to give 4-di-allylaminoethyl-2(3H)-indolone. This material (1 g) is dissolved in ether-ethanol and treated with methane sulfonic acid to give the methane sulfonate salt. Using benzyl bromide gives 4-dibenzylaminoethyl-2(3H)-indolone.

EXAMPLE 8

Anhydrous tetrahydrofuran (10 cc) at 20° under nitrogen was treated with 2.0 cc (4.8 mm) of 2.4 M n-butyl lithium in hexane followed by 0.49 g (1.5 mm) of 4-di-n-propylaminoethyl-7-methoxy-2(3H)-indolone hydrochloride and 0.349 g (3 mm) of N,N,N',N'-tetramethylethylenediamine. Gas evolution and dissolution of the salt was observed.

The reaction mixture was cooled in a dry ice-propanol bath and treated with 1.5 mm of iodomethane in one portion. After stirring in the cold for 10 minutes, the bath was removed and stirring continued for 2 hours. The mixture was quenched in 20 cc of saturated ammonium chloride solution, diluted with ethyl ether. The organic layer was separated. The remaining material was again extracted twice. The combined dried extracts were concentrated in vacuo, stripped from ethyl ether and carbon tetrachloride.

Analysis of the solid demonstrated a mixture of 10% starting material and a 50-50 mixture of di- and mono 33 3-methylated product. The mixture was realkylated to give 169 mg of 3,3-dimethyl-4-di-n-propylaminoethyl-7-methoxy-2(3H)-indolone.

This material is hydrolyzed as described in U.S. Pat. No. 4,314,944, Example 4 then, dehydroxylated in the 60 form of the crude product as described above to give 3,3-dimethyl-4-di-n-propylaminoethyl-2(3H)-indolone hydrochloride.

The Kende process was repeated using the same quantities but using 0.61 cc (9.8 mm) of methyl iodide at 65 -70°. The mixture was allowed to warm to -25° and held there for 1 hour followed by 3 hours at room temperature. After working up as described, 4-di-n-

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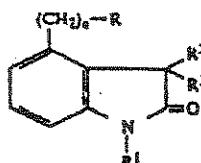
propylaminoethyl-7-methoxy-3-methyl-2(3H)-indolone was recovered. This is treated with boron tribromide and, then, 5-chloro-1-phenyl-1H-tetrazole to give 4-di-n-propylaminoethyl-3-methyl-2(3H)-indolone hydrochloride.

EXAMPLE 9

4-(2-di-n-Propylaminoethyl)-2(3H)-indolone hydrochloride (125 mg) is mixed with 200 mg of lactose and 2 mg of magnesium stearate, filled into a hard gelatin capsule and administered to a hypertensive patient from 1-3 times daily.

What is claimed is:

1. A compound of the structural formula:



in which:

R is amino, C1-6-lower alkylamino, di-(C1-6-lower alkyl)amino, allylamino, diallylamino, N-(C1-6-lower alkyl)-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethyl amino or di-(4-hydroxyphenethyl)amino, and

R¹, R² and R³ are, each, hydrogen or C1-6-lower alkyl; or a pharmaceutically acceptable, acid addition salt thereof.

35 2. The compound of claim 1 in which R¹, R² and R³ are hydrogen, n is 2 and R is amino, di-n-propylamino, n-propyl-n-butylamino or 4-hydroxyphenethylamino.

3. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

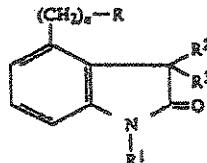
4. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone as the free base.

5. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride.

6. The compound of claim 1 being 4-(2-aminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

7. The compound of claim 1 being 4-(4-hydroxyphenethylaminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

8. A pharmaceutical composition having D₂ receptor agonist activity comprising a nontoxic, agonist quantity of a compound of the structural formula:



in which:

R is amino, C1-6-lower alkylamino, di-(C1-6-lower alkyl)amino, allylamino, diallylamino, N-(C1-6-lower alkyl)-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-

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hydroxyphenethylamino or di-(4-hydroxyphenyl)amino, and
R¹, R² and R³ are each hydrogen or C₁₋₄-lower alkyl; or a pharmaceutically acceptable acid addition salt thereof, in dosage unit form, combined with a pharmaceutical carrier.
9. The composition of claim 8 in which the D₂-agonist compound is 4-(2-di-n-propylaminoethyl)-2(3H)-

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indolone or a pharmaceutically acceptable, acid addition salt thereof.

10. The composition of claim 8 in which the D₂-agonist compound is 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride.

11. The composition of claim 8 in dosage unit form, adapted for use as an antihypertensive composition.

12. The composition of claim 8 in which the quantity per dosage unit is selected from the range of 50-500 mg base weight of said compound.

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ATTACHMENT E

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,452,808

DATED : June 5, 1984

INVENTOR(S) : Gregory Gallagher, Jr.

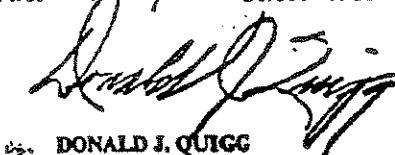
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 1 at column 10 line 25 of the patent, after
"in which:" and before "R is ..." insert -- n is 1-3, -- .

In claim 8 at column 10 line 64 of the patent, after
"in which:" and before "R is ..." insert -- n is 1-3, -- .

Signed and Sealed this

First Day of October 1985



Mr. DONALD J. QUIGG

Commissioner of Patents and
Trademarks—Designate

Attest:

Ruth C. Mason
Attesting Officer

